I. Amendment of claims:

a) Please cancel claims 61-63, 69-80, 82-86, 89-99, 103-111, 113-116, and 118-122, without prejudice.

b) Please amend the claims as indicated below. For the convenience of the Examiner, a copy of the complete set of pending claims, in the form they will take after entrance of the present Amendment is included herewith at the end of the Response.

59. (Twice Amended) A pharmaceutical composition for delivering [comprising] a therapeutically effective amount of an epothilone to a mammal, the pharmaceutical composition comprising: an epothilone and a pharmaceutically acceptable carrier, wherein the [therapeutically effective] amount of the epothilone in carrier is [an amount] sufficient for the composition to deliver to the mammal between about 0.001 mg to about 40 mg epothilone per kg body weight.

64. (Twice Amended) A method of treating cancer in a subject comprising:

administering a therapeutically effective amount of an epothilone to a subject in need thereof, wherein the therapeutically effective amount of the epothilone is an amount [sufficient to deliver] between about 0.001 mg to about 40 mg epothilone per [kg] kilogram of the subject's body weight.

87. (Twice Amended) A method of [killing tumor cells or] inhibiting [the] growth of a tumor [cells] in an animal comprising:

[contacting tumor cells with] administering to an animal that has tumor an amount of a composition comprising an epothilone, the amount being effective to [kill tumor cells or] inhibit [the] growth of the tumor [cells] without administration of the composition killing the animal, wherein the amount of the [epothilone] composition is an amount sufficient to deliver about 0.001 to about 40 mg epothilone per [kg] kilogram body weight.

100. (Amended) The pharmaceutical composition of claim 59 [96], wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.01 to about 40 mg epothilone per kg body weight.

101. The pharmaceutical composition of claim 59 [96], wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.001 to about 25 mg epothilone per kg body weight.

102. The pharmaceutical composition of claim 59 [96], wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.01 to about 25 mg epothilone per kg body weight.

112. (Amended) The method of claim [80] 64, wherein the [step of administering comprises administering multiple times a therapeutically effective amount of a composition comprising an epothilone, wherein the therapeutically effective amount is an amount sufficient to deliver about 0.001 to about 40 mg epothilone per kg body weight] amount is administered to the subject at least twice in a seven-day period.

117. (Amended) The method of claim 64, wherein the step of administering comprises:

administering [in multiple] at least two doses of a therapeutically effective amount of an epothilone to a subject in need thereof, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.001 mg to about 40 mg epothilone per [kg] kilogram body weight.

II. Rejection under 35 U.S.C § 112:

The Examiner has rejected claims 75-79, 85-87, 89-95, 115-116, and 121-122 under 35 U.S.C. § 112, first paragraph, as not being enabling for "inhibition" but being enabling for apoptosis (cell death). Applicant respectfully submits that although the mechanism by which epothilones inhibit the growth of a tumor may involve apoptosis, the mechanism is not material

to enablement. As pointed out in the Response mailed July 16, 2002, the Specification provides ample evidence that epothilones are capable of killing cells or inhibiting the growth of various tumor cell lines (see, for example, pages 63-47; and Tables 5 and 7). The Specification also includes data from several mouse models of cancer (see Tables 11, 12, and 13) demonstrating that epothilone B has been shown to decrease tumor volume. The Specification is therefore fully supportive of the amended claims directed to a method of treating cancer and a method of inhibiting the growth of a tumor in an animal. Applicant requests that the rejection be removed.

III. Rejection under 35 U.S.C. § 103(a):

The Examiner has rejected claims 59-95 under 35 U.S.C. § 103(a) as being unpatentable over the Bollag *et al.* reference (*Cancer Res.*, Vol. 55 (1995), pages 2325-2333). The Examiner asserts that the Bollag *et al.* reference teaches "epothilones A and B, their compositions as an oily residue (column 2, page 2326) and methods of use for treating cancer or tumor and particularly multiple drug-resistant cells. (See column 2, page 2331)." The Examiner further asserts that the Bollag *et al.* reference teaches "the method of use of epothilones in combination with taxol (a cytotoxic agent). See column 2, page 2328 to column 1, page 2330." In the section entitled "Ascertainment of the difference between the prior art and the claims" the Examiner states that "applicants are claiming effective amounts of epothilones from about 0.001 to about 40 mg/kg of body weight, and administration of the effective dose to a subject multiple times." In the section labeled "Finding of *prima facie* obviousness—rational and motivation" the Examiner then asserts that "for the Bollag *et al.*, to use epothilones for the treatment of cancer or tumors, effective amount must necessarily be used," and states that Applicant's "claiming variable effective amounts of epothilones, and administration of the effective dose to a subject multiple times, is not in and of itself patentable over the prior art of Bollag *et al.*" The Examiner further states that "the motivation is in the expectation that the epothilone compositions would be effective for the treatment of cancer given the experimentation performed by Bollag *et al.*, and results thereof."

Applicant respectfully traverses this rejection. Bollag *et al.* demonstrates that Epo A and Epo B are cytotoxic to certain cultured cell lines including HeLa cells, Hs578T cells, and

multiple-drug resistant cells. Many compounds are cytotoxic in such *in vitro* studies. Precious few prove to be useful as therapeutics. Most typically, the difficulty with cytotoxic compounds is that it is not possible to administer them in an amount that will kill tumor cells without also killing the host organism. Thus, the teachings of Bollag *et al.* provide, *at most* a suggestion that it might be desirable to *try* to find an amount of an epothilone that could be therapeutically effective. There is no reasonable expectation that such an amount exists and can be found. As discussed in the prior Response of July 16, 2002, the Bollag *et al.* reference itself viewed their own results as an invitation to experiment and not a demonstration of a pharmaceutically useful or effective composition.

Furthermore, as discussed in the in-person interview on November 19, 2002, the present inventors, who are of at least of ordinary skill in the art, could not readily identify a therapeutically effective range of Epo A or Epo B based on Bollag *et al*'s description, which does not even suggest a therapeutically effective concentration of epothilone necessary to treat cancer in a subject. Using *in vivo* studies in mice, Applicant did discover a therapeutically effective range from about 0.001 mg to about 40 mg epothilone per kg body weight. Initial studies of administering epothilone compounds to mice led unexpectedly to all the mice being killed. However, the inventors of the present application after many experiments were able to demonstrate that epothilones compounds could be used in the treatment of cancer at the therapeutically effective concentration claimed.

For all the reasons set forth above, the claimed pharmaceutical compositions and methods of treating cancer cannot be rendered obvious by the limited teachings of Bollag *et al.*

IV. Double Patenting Rejection.

Examiner has provisionally rejected claims 59, 61-64, 66-80, 82-87, and 89-95 under 35 U.S.C. § 101 as claiming the same invention as that of claims of co-pending application USSN 09/874,514 (the '514 application). Applicant respectfully submits that since the last Office Action, the claims of both the present application and those of the '514 application have been amended and that the currently pending claims in each application do not recite the same invention. Applicant respectfully refrains from further addressing this issue until such time as